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Prüfungsantrag gem. § 44 PatG ist gestellt

(54) Behandlung der Hyperlipidämie und Herstellung eines Arzneimittels hierfür

Es wird eine Behandlung der Hyperlipidämie und die Herstellung eines Arzneimittels hierfür vorgeschlagen. Dabei wird erfindungsgemäß Dehydroepiandrosteron oder ein Derivat hiervon als Wirkstoff eingesetzt, dessen Metabolismus in Figur 2 veranschaulicht ist.

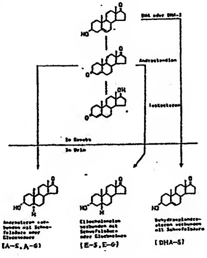

FIG. 2

DE 3826297 A1

M/542,989

L9 ANSWER 23 OF 27 CAPLUS COPYRIGHT 2007 ACS on STN
AN 1989:609762 CAPLUS
DN 111:209762
TI Treatment of **hyperlipidemia** with dehydroepiandrosterone
IN Nishikaze, Osamu; Hayashi, Yoshio
PA Daiichi Pharmaceutical Mfg. Co., Ltd., Japan
SO Ger. Offen., 14 pp.
CODEN: GWXXBX
DT Patent
LA German
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	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
PI	DE 3826297	A1	19890216	DE 1988-3826297	19880803	<--
	JP 01040428	A	19890210	JP 1987-197735	19870807	<--
	AU 8820302	A	19890209	AU 1988-20302	19880802	<--
	AU 616423	B2	19911031			
	FR 2619009	A1	19890210	FR 1988-10704	19880808	<--
	FR 2619009	B1	19940923			
	GB 2208473	A	19890405	GB 1988-18776	19880808	<--
PRAI	JP 1987-197735	A	19870807			

AB Dehydroepiandrosterone (I) and its derivs. are drugs for the treatment of **hyperlipidemia**. Tablets comprised I 25, lactose 80, starch 12.5, polyvinylpyrrolidone-K30 5 and Mg stearate 5 mg. Daily administration of 1 tablet/day to humans, for 14 days, decreased in the blood serum the β-lipoprotein, triglycerides, phospholipids, nonesterified fatty acids and cholesterol levels. I had no side effects.

TI Treatment of **hyperlipidemia** with dehydroepiandrosterone
PI DE 3826297 A1 19890216

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IT **53-43-0**, Dehydroepiandrosterone 53-43-0D,
Dehydroepiandrosterone, derivs. 1099-87-2
RL: BIOL (Biological study)
(**hyperlipidemia** treatment by)

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Result Page

The available invention concerns a treatment of the Hyperlipidämie with humans and animal and the production of a pharmaceutical composition for this.

With the Hyperlipidämie acts it around a condition, with that the content of the blood at Lipiden due to an excessive admission of Lipiden such as Cholesterin, Neutralfetten etc. or according to an abnormal Lipometabolismus is too high. For all these cases the designation Hyperlipidämie is completely generally used.

In the following table 1 the normal values are and/or. Ranges for the serum Lipidgehalt and - Lipoproteingehalt with humans indicated.
< tb> < TABLE> Columns=2 of normal ranges for the serum Lipidgehalt and - Lipoproteingehalt with humans
< tb> Head Col 1: Kind
< tb> Head Col 2: Normal range
< tb> Entire Cholesterin< SEP> 115-211 mg/dl
< tb> Triglyceride< SEP> 35-160 mg/dl
< tb> Phospholipide< SEP> 159-299 mg/dl
< tb> Chylomicron< SEP> 0 (with hunger)
< tb> VLDL< SEP> 20-400 mg/dl
< tb> (VLDL Chol.) < SEP> less than 30 mg/dl
< tb> LDL< SEP> 200-400 mg/dl
< tb> (LDL Chol.) < SEP> less than 170 mg/dl
< tb> HDL
< tb> männlich< SEP> 125-425 mg/dl
< tb> (HDL Chol.) < SEP> 37-57 mg/dl
< tb> weiblich< SEP> 250-650 mg/dl
< tb> (HDL Chol.) < SEP> 36-70 mg/dl
< tb> Lipoproteinfraktion
< tb> alpha - Lipoprotein (HDL) < SEP> 20.0-50.0%
< tb> Pr3 beta - Lipoprotein (VLDL) < SEP> 8.5-19.9%
< tb> beta - Lipoprotein (LDL) < SEP> 37.1-54.7%
< tb> < /TABLE>

(Tokyo Medical and Dental University)

In the following table 2 the physikochemischen characteristics and the composition of these Lipoproteine are indicated.

Table 2

Physikochemi characteristics and composition of Lipoprotein

▲ topEMI4.1

With the Hyperlipidämie differentiates one the Hyperchylomicronämie, Hypercholesterämie, Hypertriglyceridämie etc. depending upon kind and concentration of the Lipide. WHO (World Health Organization) classifies the Hyperlipidämie according to the 6 3 types indicated in the following table depending upon the condition of the Lipoproteine. The Hyperlipidämie is observed generally with humans middle and higher age. It leads to a deposit of the Lipide on the Arterienwänden or in the interior connective tissues. The Hyperlipidämie observed with younger humans is to be mostly due to a metabolic malfunction, which has its cause in the hereditary factors and family Hyperlipidämie is called. The Hyperlipidämie stands for the Koronararterien, Basisarterien etc. in close relationship with the Arteriosklerose and very often causes a pulsatische (pultaceous) Sklerose in the Aorta. Very frequently it arises in the Koronararterien and causes angina pectoris and myocardiale Infarkte. Finally also an inclination to the Cholelithiasis exists with a Hyperlipidämie.

As previously mentioned, the Hyperlipidämie in vascular disturbances expresses itself such as Arteriosklerose. It is therefore necessary to seize therapeutic measures in order to carry for these causes calculation. These measures can be divided as follows:

(1) In order to treat the food-conditioned Hyperlipidämie, which is due to excessive admission of Lipiden or Cholesterin, a food therapy is recommended by reduction of food intake or kinetics therapy by increase of the energy use. If these methods lead to no satisfying results, a pharmaceutical therapy is to be considered.
(2) In order to treat the family Hyperlipidämie due to hereditary factors, in a disturbance for the Lipometabolismus, which Apoprotein or receptor mechanism responsible person enzyme function expresses, a pharmaceutical therapy is by administration of medicaments application.
(3) To the treatment of the secondary Hyperlipidämie, those by other diseases such as Nephrose, diabetes etc. verursacht wird, sollten die therapeutischen Methoden darauf ausgerichtet werden, die Ursachen für diese Krankheiten zu

eliminieren, um so die pathologische Situation bei den Basiskrankheiten zu verbessern.

With the medicaments used in the pharmaceutical therapy it acts and. A. around such, which inhibieren the intrakorporale absorption of Cholesterin as well as the biosynthesis of Cholesterin, as well as around medicines for the improvement of the Lipometabolismus. Which concerns the absorption inhibitors, then it concerns here over out of a anionischen exchanger resin resulting Cholesterylamin, Melinamid, and Sojasterol, derived from the Linolsäureamid, a unverselfte substance of the soy bean oil. As biosynthesis inhibitors pro baking oil and Clofibrat preparations are far common. To those substances, which improve the Lipometabolismus, belong Heparin, Dextran sulfuric acid etc., which increases the activity of the Lipoproteinlipase and which Katabolismus of the Lipoproteine improve.

It is however well-known that these medicines exhibit side effects, like easy symptoms in the digestive tract (Cholesterin absorption inhibitor), malfunctions in the liver, malfunctions in the digestive tract, Cholelithiasis (Cholesterin biosynthesis inhibitor) etc.

It was now found that Dehydroepiandrosteron (DHA) and Dehydroepiandrosteron sulfate (DHAS) exhibit a outstanding anti- Hyperlipidämi effect. With the therapy at humans and the effects determined thereby and side effects accomplished with the DHA containing pharmaceutical preparing an acceptance of the Hyperlipidämie, a stabilization of the vascular wall and a Enfernung of to these hanging Thrombozyten were determined. Side effects assumed first were not observed.

The invention is described in the following with reference to the two figures, by those

Fig. 1 the expiration of synthesis of the Nebennierenrindensteroide and

Fig. 2 the metabolic mechanism of Dehydroepiandrosteron illustrates.

As follows from the managing description, the invention refers to antihyperlipidämisches means, which contains DHA or a derivative of it as active substance. By a DHA derivative is to be understood in this connection in particular a connection between DHA and sulfuric acid and similar products.

With DHA it concerns a well-known chemical substance. It represents one the Steroidhormone, which becomes seperate from this in the suprarenal body crust produced and. As derivative of DHA also by Veresterung of the hydroxyl group of the DHA in 3-Stellung received connection is possible. A typical example of a DHA derivative in the sense of the invention is a connection between DHA and sulfuric acid, which represent a urophanischen type. The invention is not limited however to these derivatives; it extends also to others, if necessary. by synthesis received derivatives.

In the following the characteristics of DHA and DHA sodium sulfate are indicated.

(1) Dehydroepiandrosteron (DHA)
EMI9.1

(2) Dehydroepiandrosteron sodium sulfate (DHA-S)
EMI10.1

With oral application the normal dose of DHA and its derivatives is between 25-75 mg/day. In individual cases the dose depends on sex, age, the degree of the Fettleibigkeit and other symptoms.

As pharmaceutical preparation for the oral application of the active substance according to invention tablets, caps, granulates, powder etc. come. in consideration. These preparing can be manufactured according to the usual pharmaceutical methods.

The approximate expiration of synthesis from Nebennierenrindensteroiden is in the Fig. 1 shown. So far about 50 different Steroidhormone from the biosynthesis of the suprarenal body crust were isolated. From the table 4 its rough organization follows, i.e. in Glucocorticoid, which stands in biochemical regard in relationship to the Saccharometabolismus (z. B. Cortisol), Mineralcorticoid, which stands in relationship to the electrolytic Metabolismus (z. B. Aldosteron) and androgen [DHA and with sulfuric acid connected DHA (DHA-S)].

Table 4

Steroid from the human suprarenal body crust
EMI11.1

DHA is produced from DHA-S. For this reason DHA-S is called supply hormone of DHA. With DHA it concerns a Steroid, which can be biosynthetic origin from androgens hormones such as Testosteron and Östradiol; Testosteron and Östradiol are produced however in the suprarenal body crust only in small quantities.

DHA is effective only to very small extent as Sexualhormon. It shows effects on the Lipometabolismus and Proteinmetabolismus and practices also an influence on the Salzmetabolismus such as phosphoric acid, potassium, sodium etc. out. As from Fig. 2, it comes out in the urine as DHA-S is separated. In addition, it takes place an elimination in the form of Androsteron or Etiocholanolon, bound at sulfuric acid or Gluconsäure, whereby the mechanism over Androstendion runs. All these substances can be called 17-KS (Ketosteroide). With (non-pregnant women) women it is accepted that nearly everything originates these 17 KS min s from the suprarenal body crust. With men come 2/3 to 3/4 this Steroide from the suprarenal body crust, while the remaining 1/3 to 1/4 in the testicles are produced.

It could be shown on experimental way that the quantity of the Stoffwechselprodukte of DHA (17-KS in the urine), separated with the urine, is small with a patient with Hyperlipidämie. With diabetes and other diseases in connection with Fettleibigkeit an extremely small quantity was found.

DHA and DHA-S (type of supply of DHA) come plentifully in the blood of younger humans (at the age of 20 to 30 years) before and with increasing age remove the values gradually. In contrast to this Cortisol becomes nearly in continuous quantity (15,-20 mg/day) seperately, independently of the age, whereby as its metabolite 17-OHCS (Hydroxycorticoid) in the urine it is separated.

DHA inhibiert the synthesis of Lipiden and reduces the quantity of Cholesterin and Lipiden in the blood, while excessive

secretion promotes the synthesis of Lipiden connected by Cortisol, with a very strong insulin secretion directed against it. Accordingly Cortisol and insulin no more cannot be held or inhibiert under control with reduction of the DHA secretion as consequence of the age or for other reasons, so that a gradual Lipidanreicherung in the fatty tissue begins. This leads to the Fettleibigkeit, causes disturbances in the production and secretion of insulin and has finally diabetes to the consequence.

DHA causes a Inhibierung and control of the production of insulin and Cortisol at the same time. Additionally it prevents a blood coagulation and an aggregation of the blood panels.

With oral administration DHA arrives into the intestine and into DHA-S is converted there. In this form it is carried to the different fabrics and reconverted then again into DHA. This inhibiert the activity of the enzyme Glucose-6-Phosphatdehydrogenase (G6PDH), which stands in close relationship to the Steatogenese. This entails antihyperlipidämische effects. Another outstanding characteristic of DHA consists of the fact that with practical testing no side effects were determined.

The antihyperlipidämischen effects of DHA show up not only with humans but also with domestic animals and animals in the zoo. It concerns thus a useful antihyperlipidämisches means both for humans and animals.

In the following manufacture examples of the antilipidämische means according to invention, bioassays, acute are described toxicity and clinical tests.
< tb> < TABLE> Columns=2> Manufacture example 1 DHA tablet
< tb> Head Col 1: Composition of the tablet
< tb> DHA (Dehydroepiandrosteron) < SEP> 25 mg
< tb> Laktose< SEP> 80 mg
< tb> Stärke< SEP> 12.5 mg
< tb> Polyvinylpyrrolidon-K30< SEP> 5 mg
< tb> Magnesiumstearat< SEP> 2.5 mg
< tb> Gesamt< SEP> 125 mg
< tb> < /TABLE>

Method of the tablet production: Wet granulation method
Tablet diameter: 7 mm
Appearance: white tablet
< tb> < TABLE> Columns=2> Manufacture example 2 DHA S tablet
< tb> Head Col 1: Composition of the tablet
< tb> DHA-S (Dehydroepiandrosteron sodium sulfate) < SEP> 35 mg
< tb> Laktose< SEP> 70 mg
< tb> Stärke< SEP> 12.5 mg
< tb> Polyvinylpyrrolidon-K30< SEP> 5 mg
< tb> Magnesiumstearat< SEP> 2.5 mg
< tb> Gesamt< SEP> 125 mg
< tb> < /TABLE>

Method of the tablet production: Wet granulation method
Tablet diameter: 7 mm
Appearance: white tablet
35 mg DHA-S are equivalent to 25 mg DHA

Animal test

Twenty adults SD-rats (10 male rats and ten female rats) were used, whereby these were divided in the control and the group of tests.

The DHA containing fodder (0.6%) was given to the group of tests and fodder without DHA of the control's group during one duration of 11 weeks. From this the rats were tested.

The composition of the rat body at the group, which DHA was given, is indicated in the table 5.

Table 5
EMI15.1

It became far influence of DHA on the liver weight, which examines G6PDH activity in the liver fabric and the Triglyceride in the serum. The results are indicated in the following table 6.

Table 6
EMI15.2

Acute toxicity test

DHA was given subkutan or to orally male and female ICR mice and SD-rats and the LD50 (mg/kg) is determined. The results are indicated in table 7.

Table 7
EMI16.1

With the chronic toxicity tests with mice and rats in no case a pathological change was observed.

Clinical test 1

With five patients with Hyperlipidämie a clinical test was accomplished. Older, sex, Lipidgehalt of the blood etc. are indicated in the following table 8. For the test DHA tablets were used, which were manufactured according to the managing manufacture example 1, whereby each tablet contained 25 mg DHA. To each meal, thus three times daily, a

tablet was given (75 mg DHA per day). The administration period varied between 3 and 5 months, depending upon the symptoms. During this time the use of another medicament was avoided.

Table 8
EM17.1

Clinical test 2

Further a clinical test with 5 women was accomplished. DHA was given again in form of the mentioned tablets. Per day a tablet was given (25 mg DHA per day). The table 9 shows the test results proving an improvement of the Lipidgehaltes in the blood. As with the clinical test 1 also in this case during the testing time area the income of other medicaments was already avoided. In all cases the values for the Triglyceride, Phospholipide and such a thing, were lowered which lay outside of the normal ranges, thus that values resulted within the normal ranges, so that herein a confirmation for it could be seen that DHA exhibits an excellent antihyperlipidämische effect.

As the managing description shows, the administration of the antihyperlipidämischen means leads in accordance with the invention at patients to the fact that its effect component DHA or its derivative normalizes the Lipidmetabolismus improved and the Lipidspiegel in the blood. As result of it the blood vessel walls are strengthened, so that both a Arteriosklerose and an angina are avoided pectoris and a myokardialer Infarkt with humans and animal.

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Result Page

1. Use of Dehydroepiandrosteron or its derivatives for the production of a medicament against Hyperlipidämie.

2. Application of an effective quantity of Dehydroepiandrosteron or its derivatives apart from a vehicle, a diluent or a support for the therapeutic treatment of the Hyperlipidämie with humans or animal.

3. Use according to requirement 1 or application according to requirement 2, by the fact characterized that the derivative is a connection received by Veresterung of the hydroxyl group in 3-Stellung of the Dehydroepiandrosterons.

4. Use according to requirement 1 or application according to requirement 2, by the fact characterized that the derivative represents a connection between Dehydroepiandrosteron and sulfuric acid.

5. Application according to requirement 2, by the fact characterized that the Dehydroepiandrosteron or the derivative is given of it in a dose 25-75 mg/day/human being.

6. Application according to requirement 2, by the fact characterized that the Dehydroepiandrosteron or its derivative is orally given.

7. Application according to requirement 2, by the fact characterized that the Dehydroepiandrosteron or its derivative is given in the form of tablets, caps, granulates or powder.

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